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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/035,596	03/05/98	GUNZBURG W	GSF98-01

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EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	7

DATE MAILED: 06/08/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/035,596	Gunzburg et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-40 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-40 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application is a 371 of PCT/EP96/03922 filed 9-6-96. The applicant claims priority of foreign application in Denmark 0976/95 filed 9-6-95.

Priority

1. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark 0976/95 on 9-6-95. It is noted, however, that applicant has not filed a certified copy of the foreign application as required by 35 U.S.C. 119(b).

Filing of a certified copy of the foreign application is required for the benefit of the foreign priority.

Specification

In the beginning of the specification, it should be noted that this application is a **371** of PCT/EP96/03922, not a **continuation** of PCT/EP96/03922. Correction is required.

There is no brief description of drawing in the specification. Brief description of drawing is required in the specification.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 17 encompasses cells contained within human beings, which are not considered patentable subject matter. See MPEP 2105. This rejection could be overcome by amending the claim to recite "an isolated human cell" for example.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-12, 15, 16, 18-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1-12, 15, 16, 18-40 are directed to a DNA construct or a recombinant viral vector comprising at least one therapeutic gene under transcriptional control of the WAP or MMTV regulatory sequences, retroviral particle or cells containing said DNA construct or viral vector, encapsulated cells comprising a core containing said cells and a method of using said viral

vector, said retrovirus, said cells or said encapsulated cells for the treatment of disorders or diseases of human mammary cells, including human mammary carcinoma *in vitro* or *in vivo.* Claims 1-12, 15, 16, 18-25 recite the limitations for the treatment of disorders or diseases of human mammary cells in vivo. Claims 26-36 read on the expression of therapeutic genes in vivo to exhibit therapeutic effects in human mammary cells.

The specification of the instant invention discloses the construction of vectors pMMTV-BAG and pWAP-BAG containing β-galactosidase gene under the control of MMTV and WAP, respectively. The specification shows the expression of β-galactosidase in explanted normal primary human mammary tissue infected with virus containing said vectors set forth above. The specification fails to provide adequate guidance and data for the treatment of disorders or disease of human mammary cells with the DNA construct, retrovirus, cells and encapsulated cells set forth above and show the therapeutic effect of said treatment *in vitro* or *in vivo*.

The state of the art of gene therapy at the time of the invention is unpredictable. Orkin et al. 1995 (X) reported that none of the available vector systems for gene transfer is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Retrovirus infects and integrates only dividing cells, other problems include cumbersome preparation and relatively low titer, size constraints on inserted genes, and the potential for genetic damage due to random integration in the host genome. Adenovirus, Herpesvirus and poxvirus all have the problem of relatively high immunogenicity and complexity of its genome. Adeno-associated virus requires replicating adenovirus to grow and no helper cell

line available. Direct administration of DNA or DNA complexes (e.g., liposomes) has disadvantages of lower efficiency of gene transfer (compared with viruses) and the absence of mechanisms for specifically maintaining the introduced DNA within the cell. In terms of the small scale clinical experiment which is referred to as "clinical trials", the efficacy has not been established for any gene therapy protocol, adverse short term effects related to gene transfer protocols appears to vary, depending on the nature of the virus used as a vector and the patient to which it is administered. Because clinical experience is still so limited, it is not possible to exclude longterm adverse effects of gene transfer therapy, the multiple integration events resulting from repeated administration of large doses of retroviruses theoretically pose a risk for leukemic transformation. It is not always possible to extrapolate results from experiments in non-human animals to human studies.

The feasibility of encapsulated cells for the treatment of disorder or disease of human mammary cells is still unknown at the time of the invention. Aebischer et al., 1991 (U3) encapsulated PC12 cells in polyelectrolyte-based microcapsules or thermoplastic-based macrocapsules and maintain *in vitro* or transplanted in a rat experimental Parkinson model for 4 weeks. They point out that unencapsulated PC12 cells can lead to the formation of lethal tumors in rats, and do not survive if transplanted into the nervous system of either guinea pigs or mice. The presence within the microcapsule core of a hydrogel possibly impeded cell movement within the capsule, resulting in densely-packed cell aggregates and because their poor mechanical properties, microcapsules are more difficult to implant. Often the implanted microcapsules lost

their spherical shape and the retrieval of microcapsules is not possible without significant injury to the brain. In addition, alginate-like materials is found in the vicinity of some microcapsules rasing questions about the stability of the microcapsules *in vivo*. It is also unclear that if the encapsulated cells will grow within the microcapsule, although the encapsulated cells does not trigger immune response from the host as shown by Aebischer et al., if the cells continue to grow within the microcapsule, it is possible the cells could burst out of microcapsule and trigger immune response. Because the claimed invention encompasses any type of cells containing therapeutic gene under the control of WAP or MMTV promoter for the treatment of disease of human mammary cells, administration of cells into immunologically incompatible host, between different species or different individual in same species for example, would stimulate immune response from the host and pose safety problem. Without the adequate guidance and therapeutic data of using cells or encapsulated cells for treating disease of human mammary cells *in vitro* and *in vivo*, it is unpredictable if cells or encapsulated cells containing any therapeutic gene would exhibit any therapeutic effect on treating disease of human mammary cells without any safety problem or unforseen difficulties.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to have made a DNA construct or a recombinant viral vector comprising at least one therapeutic gene under transcriptional control of the WAP or MMTV regulatory sequences, retroviral particle or cells containing said DNA construct or viral vector, encapsulated cells comprising a core containing said cells to treat disorders or diseases of

human mammary cells, including human mammary carcinoma and show therapeutic effect of said treatment *in vivo*. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-22 and 26-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-19 are vague and indefinite because it is unclear how or whether the recitation of the intended use would limit the claimed vector and/or cells.

Claims 7-9, 12, 21, 24, 34-36 and 38 are vague and indefinite because there is no antecedent basis for the term "said viral vector".

Claim 13 is vague and indefinite because it is unclear whether a retroviral provirus alone or a retroviral provirus integrated in the vicinity of the human genome is intended to be claimed.

Regarding claims 11 and 32, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 20-22 and 26-36 provides for the use of DNA construct, recombinant viral particle and cells, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 36 recites the limitation "said deleted region" in line 5 and 6 of the claim. There is no antecedent basis for this limitation in the claim.

Claims 37-40 are vague and indefinite because the claims recite incomplete method. The essential steps of a method is missing: How and where the medicament is to be administered to a human, is the therapeutic gene being expressed, is sufficient amount of therapeutic product present in target site, and if the therapeutic product present for sufficient duration of time to be exhibit therapeutic effect.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Gunzburg et al., 1991(U) or Velander et al., 1992(V).

Claims 1-3 and 6 are directed to a DNA construct comprising at least one therapeutic gene under the transcriptional control of the WAP regulatory sequences. It is noted that the claims recite an intended use for treatment, however such "use" does not afloat the compound/composition being claimed. Therefore, the instant rejection applies to claimed compound/composition.

Gunzburg et al. produced a plasmid vector containing human growth hormone (hGH) under the control of WAP promoter for the expression of hGH in transgenic mice (see e.g. abstract and page 124, Fig. 1).

Velander et al. constructed a plasmid DNA containing human protein C under the control of WAP promoter for the expression of protein C in transgenic swine (see e.g. abstract and page 12004, Fig. 1). Therefore, califs 1-3 and 6 are clearly anticipated by Gunzburg et al..

9. Claims 1 and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Ricketts et al., 1992(W).

Claims 1 and 4-6 are directed to a DNA construct comprising at least one therapeutic gene under transcriptional control of the MMTV regulatory sequences.

Ricketts et al. constructed a plasmid containing P450c21 gene under the control of MMTV-LTR for the expression of P450c21 in cultured COS-1 cells (see e.g. abstract). Thus claims 1 and 4-6 are clearly anticipated by Ricketts et al..

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-17, 23-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dranoff et al., 1993 (U2) in view of Lefebvre et al., 1991 (V2), Paleyanda et al., 1994 (W2) and Meade et al., 1989, US Pat. No. 4,873,316 (A).

Claims 1-17, 23-36 are directed to a DNA construct or a recombinant viral vector comprising at least one therapeutic gene under transcriptional control of the WAP or MMTV regulatory sequences, retrovirus or cells containing said viral vector and pharmaceutical composition containing said DNA construct, said retrovirus or said cells, and method of use. As far as claims 1-17 and 26-36 are concerned they are considered for the purpose of the expression of any gene product *in vitro*. It is noted that claims 23-25 recite a pharmaceutical composition, however, for purpose of the treatment rejection such a limitation has been treated as an intended use that does not limit the vector/cells per se.

Dranoff et al. teach subcloning DNA sequences encoding the cytokine such as IL-4, IL-6, g-IFN, GM-CSF, and adhesion molecules into retroviral vector MFG which contains Moloney murine leukemia virus (Mo-MuLV) long terminal repeat (LTR) and the resulting construct are introduced into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells. The transduced B16 cells are inoculated subcutaneously into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene (see e.g. abstract; result, first and second columns). Dranoff et al. do not teach using MMTV or WAP promoter for the expression of a gene product in mammary gland. Lefebvre et al. revealed the presence of MMTV promoter and the positive and negative regulatory regions upstreams of MMTV promoter (see e.g. abstract). Paleyanda et al. constructed a plasmid containing human protein C (HPC) gene under the control of mouse WAP promoter for making transgenic mouse expressing HPC, and show that the HPC mRNA is detected mainly in the mammary gland (see e.g. abstract). Meade et al. teach production of recombinant protein in mammal's milk by using expression system comprising casein promoter operatively linked to desired gene (see e.g. abstract). Because it is well known that MMTV and WAP promoter are mammary gland-specific promoter, one would have been motivated to substitute Mo-MuLV LTR with MMTV or WAP promoter to combine with any desired gene for the construction of recombinant retroviral vector, recombinant retrovirus, or cells harboring said viral vector, and for the expression of any desired gene product in vitro. It would have been obvious for a person of ordinary skill at the time of the

invention to have practiced the claimed invention with reasonable expectation of success *in vitro*. Therefore, claims 1-17 and 23-36 are rejected under 35 U.S.C. 103(a).

12. Claims 1-19 and 23-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shao et al., 1994 (X2) and Dranoff et al. 1993 (U2) in view of Lefebvre et al., 1991(V2) and Paleyanda et al., 1994 (W2).

Claims 1-19 and 23-36 are directed to a DNA construct or a recombinant viral vector comprising at least one therapeutic gene under transcriptional control of the WAP or MMTV regulatory sequences, retrovirus or cells containing said viral vector, pharmaceutical composition containing said DNA construct, said retrovirus or said cells or encapsulated cells comprising a core containing said cell, and a method of use.

Shao et al. encapsulated B16-F10 cells transduced with retrovirus containing GM-CSF gene and monitor the secretion of GM-CSF in the culture medium (see e.g. experimental). Dranoff et al. teach subcloning DNA sequences encoding the cytokine such as IL-4, IL-6, g-IFN, GM-CSF, and adhesion molecules into retroviral vector MFG which contains Moloney murine leukemia virus (Mo-MuLV) long terminal repeat (LTR) and the resulting construct are introduced into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells. The transduced B16 cells are inoculated subcutaneously into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene (see e.g. abstract; result, first and second columns). Shao et al. and Dranoff et al. do not teach using MMTV or WAP promoter for the expression of a desired gene. Lefebvre et al. revealed

the presence of MMTV promoter and the positive and negative regulatory regions upstreams of MMTV promoter (see e.g. abstract). Paleyanda et al. constructed a plasmid containing human protein C (HPC) gene under the control of mouse WAP promoter for making transgenic mouse expressing HPC, and show that the HPC mRNA is detected mainly in the mammary gland (see e.g. abstract). It is well known that MMTV and WAP promoter are mammary gland-specific promoter, one would have been motivated to substitute Mo-MuLV LTR with MMTV or WAP promoter to combine with a desired gene for the construction of recombinant retroviral vector, recombinant retrovirus, cells harboring said viral vector, and encapsulated said cells for the expression of said desired gene product. It would have been obvious for a person of ordinary skill at the time of the invention to have combined the teaching of the references set forth above and have practiced the claimed invention with reasonable expectation of success *in vitro*. Therefore, claims 1-19 and 23-36 are rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton can be reached on (703) 308-2801. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800